REMARKS

Claims 1-86 were present in the application. By the foregoing amendments, Claims 1-73, 85, and 86 have been cancelled, and new Claims 87-107 have been added. New Claims 87-94, 96-98 and 104-107 read on the elected species, (4-{2-[(4-bromophenyl)amino]-1-methylbenzimidazol-5-yloxy}(2-pyridyl))-N-methylcarboxamide (page 52, Table 3, Example 123). Support for new claim 107 is found in the specification at page 2, line 21, through page 3, line 16, page 20, lines 24-27, and elsewhere in the application as filed. In addition, Claims 74, 75, 78, and 82 have been amended to recite the elected compounds (compounds of formula (I) wherein X_1 and X_2 are each =N or NR_4) without reference to prior cancelled claims. Claims 74-84 and 87-104 are believed to be in condition for allowance. Reconsideration and favorable action is requested.

Rejection of Claim 86 Under 35 U.S.C. §101 and §112

The Examiner has rejected Claim 86 under 35 U.S.C. §101 and §112, second paragraph. By the foregoing amendment, Claim 86 has been cancelled and these rejections are now moot.

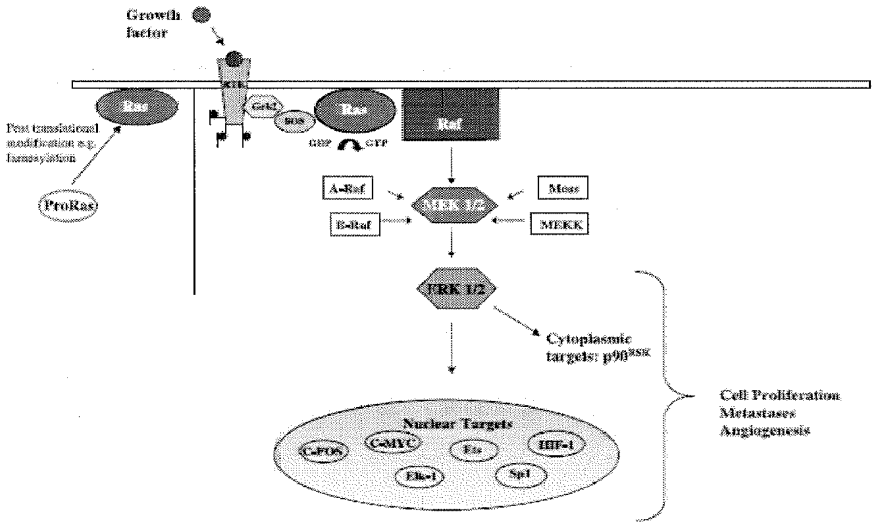
Rejection of Claims Under 35 U.S.C. §112, First Paragraph

The Examiner has rejected Claims 75-84 and 86 under 35 U.S.C. §112, first paragraph, on the basis that, "while being enabling the instant compounds represented by formulas (I) to (V) for treating some particular/specific cancer disorders, **does not reasonably provide enablement for the treating any cancer disorder in general** by inhibiting Raf kinase activity." [Emphasis in original.]

The Examiner's attention is drawn to the amendments to independent claims 75, 78, and 82 set forth herein, in which these claims are now directed to Ras/mitogen-activated protein kinase signal pathway-mediated cancer disorders; i.e., cancer disorders that are inherently mediated by inhibitors of Raf kinase activity as more fully described below. As set forth in the

LAW OFFICES OF
CHRISTENSEN O'CONNOR JOHNSON KINDNESS PLLC
1420 Fifth Avenue
Suite 2800
Seattle, Washington 98101
206.682.8100

specification[1], the Raf serine/threonine kinases are essential components of the Ras/Mitogen-Activated Protein Kinase (MAPK) signaling module that controls a complex transcriptional program in response to external cellular stimuli. Raf genes code for highly conserved serine-threonine-specific protein kinases which are known to bind to the ras oncogene. They are part of a signal transduction pathway believed to consist of receptor tyrosine kinases, p21 ras, Raf protein kinases, Mek1 (ERK activator or MAPKK) kinases and ERK (MAPK) kinases, which ultimately phosphorylate transcription factors. A schematic representation of the Ras-Raf-Erk pathway is as follows:



In this pathway, Raf kinases are activated by Ras and phosphorylate and activate two isoforms of Mitogen-Activated Protein Kinase Kinase (called Mek1 and Mek2) that are dual specificity threonine/tyrosine kinases. Both Mek isoforms activate Mitogen Activated Kinases 1 and 2 (MAPK, also called Extracellular Ligand Regulated Kinase 1 and 2 or Erk1 and Erk2). The MAPKs phosphorylate many substrates including transcription factors and in so doing set up

---

[1] See the application specification, for example, at page 1, line 16, through page 3, line 16.

LAW OFFICES OF
CHRISTENSEN O'CONNOR JOHNSON KINDNESS[PLLC]
1420 Fifth Avenue
Suite 2800
Seattle, Washington 98101
206.682.8100

their transcriptional program. Raf kinase participation in the Ras/MAPK pathway influences and regulates many cellular functions such as proliferation, differentiation, survival, oncogenic transformation, and apoptosis.

As set forth in the specification of the present application[2]:

> Since the enzyme is a downstream effector of p21ras, the instant inhibitors are useful in pharmaceutical compositions for human or veterinary use where inhibition of the raf kinase pathway is indicated, e.g., in the treatment of tumors and/or cancerous cell growth mediated by raf kinase. In particular, the compounds are useful in the treatment of human or animal, e.g., murine cancer, since the progression of these cancers is dependent upon the ras protein signal transduction cascade and therefore is susceptible to treatment by interruption of the cascade by inhibiting raf kinase activity.

Overactivation of wild-type ras and ras gene mutations, involving single amino acid substitution at codons 12, 13, or 61 leading to a constitutively active gene, have been shown to induce malignant transformation in many cancers[3]. The highest incidence of ras alterations are seen in pancreatic cancer (90%), thyroid cancer (50%), colon cancer (50%), lung cancer (30%), and acute myeloid leukemia (30%), and in some settings, may be associated with a worse overall prognosis[4]. In colon cancer, for example, the presence of K-ras mutations correlates with an

---

[2] Application specification, page 9, line 28 through page 10, line 2.

[3] Rowinsky EK et al., "Ras protein farnesyltransferase: a strategic target for anticancer therapeutic development," *J Clin Oncol* **17**:3631–52 (1999). Copies of the footnoted references are submitted herewith.

[4] Scharovsky OG et al., "Inhibition of ras oncogene: a novel approach to antineoplastic therapy," *J Biomed Sci* **7**:292–8 (2000); de Bono JS et al., "Therapeutics targeting signal transduction for patients with colorectal carcinoma," *Brit Med Bulletin* **64**:227-254 (2002).

LAW OFFICES OF
CHRISTENSEN O'CONNOR JOHNSON KINDNESS[PLLC]
1420 Fifth Avenue
Suite 2800
Seattle, Washington 98101
206.682.8100

increased risk of recurrence ($P < 0.001$) and death ($P = 0.004$), regardless of the disease stage[5]. As reported in the specification of the present application, activating mutation of one of the Ras genes can be seen in about 20% of all tumors and the Raf/MEK/ERK pathway is activated in about 30% of all tumors[6], it has been shown that B-Raf mutation in the skin nevi is a critical step in the initiation of melanocytic neoplasia[7], and more recent studies have emerged that activating mutation in the kinase domain of B-Raf occurs in about 66% of melanomas, 12% of colon carcinoma and 14% of liver cancer[8]. Thus, at the time of filing of the present application, the role Ras, and the utility of inhibitors of Raf kinase in the treatment Ras/mitogen-activated protein kinase (MAPK) signaling pathway-mediated cancers, such as melanoma, lung cancer, pancreatic cancer, thyroid cancer, bladder cancer, colon cancer, liver cancer, myeloid leukemia and villous colon adenoma, was established in the art. As stated in de Bono et al. (see footnote 2):

---

5 Andreyev HJ et al., "Kirsten ras mutations in patients with colorectal cancer: the multicenter ''RASCAL'' study," *J Natl Cancer Inst* **90:**675–84 (1998).

6 Bos, "Ras oncongenes in human cancer: a review," *Cancer Res.* **49(17)**:4682-4689 (1989); Hoshino et. al., "Constitutive activation o fthe 41-/43-kDa mitogen-activated protein kinase signaling pathway in human tumors," *Oncogene* **18(3)**:813-822 (1999).

7 Pollock et. al., "High frequency of Braf mutations in nevi," *Nature Genetics* **33**: 19-20 (2002).

8 Davies et. al., "Mutations of the BRAF gene in human cancer," *Nature* **417**:949-954 (2002); Yuen et. al., *Cancer Research* **62**:6451-6455 (2002); Brose et. al., "BRAF and RAS mutations in human lung cancer and melanoma," *Cancer Research* **62**:6997-7000 (2002).

LAW OFFICES OF
CHRISTENSEN O'CONNOR JOHNSON KINDNESS PLLC
1420 Fifth Avenue
Suite 2800
Seattle, Washington 98101
206.682.8100

> The central role in regulating these processes played by Ras and its downstream kinases, which include Raf kinase and the mitogen-activated kinases (see below), make this pathway an important target for novel anti-cancer therapeutics. . . .

The Examiner's attention is drawn to the amendments to independent claims 75, 78, and 82 set forth herein, in which these claims are now directed to Ras/mitogen-activated protein kinase signaling pathway-mediated cancer disorders; i.e., cancer disorders that are inherently mediated by inhibitors of Raf kinase activity. In view of these amendments and the comments above, it is respectively submitted that the Examiner's rejection of claims under 35 U.S.C. §112, first paragraph, should properly be withdrawn.

Rejection of Claim 74 Under 35 U.S.C. §112, First Paragraph

The Examiner has rejected Claim 74 under 35 U.S.C. §112, first paragraph, on the basis that the specification refers to Examples 1116 and 1117 (compound synthesis examples) for demonstrating Raf kinases inhibition activity and that Claim 74 reads on a mechanism of action (inhibiting Raf kinase activity), not treating specific and particular pathological conditions. As set forth above, the specification has been amended to correct the obvious clerical error in referencing example numbers, and this issue is now moot. With respect to the Examiner's suggestion that Claim 74 must refer to a specific pathological condition, this rejection is respectfully traversed.

As amended Claim 74 is directed to a method of treating a disease modulated by Raf kinase activity in a human or animal subject, comprising administering to the human or animal subject a composition comprising an amount of a compound of formula (I). Since the Examiner's rejection appears to be based on whether inhibition of Raf kinase activity (characterized by the Examiner as a mechanism of action, rather than treatment of specific and particular pathological conditions) is patentable, it appears that the Examiner's rejection is not based on failure to meet the written description requirements of 35 U.S.C. §112, first paragraph, but rather on the utility requirements of 35 U.S.C. §101. In this regard, the Examiner's attention

LAW OFFICES OF
CHRISTENSEN O'CONNOR JOHNSON KINDNESS PLLC
1420 Fifth Avenue
Suite 2800
Seattle, Washington 98101
206.682.8100

is directed to the U.S. Patent and Trademark Office's Revised Interim Utility Guidelines Training Materials (1999) at page 45, Example 8, which addresses the patentability of "therapeutics" not associated with a disease. As set forth in Example 8 of the training materials, the following claim is patentable upon the following showing:

> **Specification:** Compound A is disclosed to inhibit enzyme XYZ, a well known enzyme which is a member of the family of tyrosine kinases, *in vitro*. The specification states that compound A can be used to treat diseases caused or exacerbated by increased activity of enzyme XYZ. No actual diseases are named.
>
> **Claims:**
>
> . . .
>
> 2. A method of treating a disease caused or exacerbated by increased activity of enzyme XYZ consisting of administering an effective amount of compound A to a patient.
>
> **Analysis:** The following analysis includes the questions that need to be asked according to the guidelines and the answers to those questions based on the above facts:
>
> . . .
>
> 2) Has the applicant made any assertion of utility for the specifically claimed invention? The answer is yes. Claim 2 has the asserted utility of treating a disease caused or exacerbated by increased activity of enzyme XYZ.
>
> 3) Is the asserted utility specific? In this case, the specification teaches that the claimed compound inhibits a particular enzyme (XYZ). Therefore, compound A has properties and uses that are not applicable to a general class of compounds. Therefore, the answer is that the invention of claim 2 has a specific utility.
>
> . . .
>
> (1) Applicant provides a reference, published before the filing date of the application, which teaches that certain diseases are associated with increased activity of enzyme XYZ. In this case the examiner should withdraw the utility rejections under 35 U.S.C. § 101 and 35 U.S.C. § 112, first paragraph, for claim 2. . .

In the present application, the specification itself and the references cited therein establish the association of Ras/mitogen-activated protein kinase signaling pathway-mediated cancer disorders with Raf kinase activity and the Raf kinase inhibitors of the invention. In view of the

LAW OFFICES OF
CHRISTENSEN O'CONNOR JOHNSON KINDNESS PLLC
1420 Fifth Avenue
Suite 2800
Seattle, Washington 98101
206.682.8100

foregoing amendments, the prior art disclosed in the specification and discussed above, and the Interim Utility Guidelines, it is believed that amended Claim 74 fully satisfies the patentability requirements of 35 U.S.C. §101 and 35 U.S.C. §112, first paragraph, and that the Examiner's rejection of this claim should properly be withdrawn.

New Claims 87-107

New Claims 87-107 further define various embodiments of compounds administered in the methods of patentable independent Claims 75, 78, and 82, and are believed to be in condition for allowance.

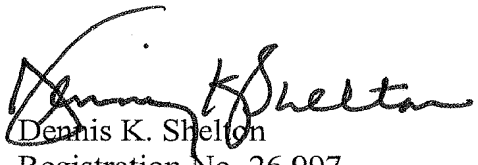
LAW OFFICES OF
CHRISTENSEN O'CONNOR JOHNSON KINDNESS PLLC
1420 Fifth Avenue
Suite 2800
Seattle, Washington 98101
206.682.8100

Conclusion

Claims 74-84 and 87-107 are believed to be in condition for allowance. Reconsideration and favorable action is requested. The Examiner is further requested to contact applicants' representative at the number set forth below to discuss any issues that may facilitate prosecution of the application.

Respectfully submitted,

CHRISTENSEN O'CONNOR
JOHNSON KINDNESS[PLLC]



Dennis K. Shelton
Registration No. 26,997
Direct Dial No. 206.695.1718

DKS:cj

LAW OFFICES OF
CHRISTENSEN O'CONNOR JOHNSON KINDNESS[PLLC]
1420 Fifth Avenue
Suite 2800
Seattle, Washington 98101
206.682.8100